Mixed Adenoneuroendocrine Carcinoma of the Gall Bladder: A Case Report of a Rare Entity
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INTRODUCTION
Gall bladder carcinoma is the most common malignancy of the extrahepatic biliary tract and stands fourth amongst the gastrointestinal cancers. Mixed adenoneuroendocrine carcinoma (MANEC), a rare entity was described and recognized by WHO in 2010. It is a rare gastrointestinal neoplasm which is characterized by the presence of at least 30% each of epithelial and neuroendocrine components. MANEC of gall bladder are exceptionally rare. There is a lack of any specific radiologic or symptomatic predictors of the tumor, and so the diagnosis is made based on the histopathological findings. We have reported a rare case of MANEC of gall bladder in a 37 year old female patient who presented with obstructive jaundice and vomiting. They have an aggressive behavior and poor prognosis. Radical surgery with adjuvant chemotherapy remains the mainstay of treatment in such cases.

Keywords: Mixed adeno-neuroendocrine carcinoma, carcinoma, gall bladder.

CASE REPORT
We present a case report of a 37 year old female patient who presented with obstructive jaundice and vomiting in the surgery department. Ultrasonography revealed thickened gall bladder wall. Patient underwent radical cholecystectomy with lymphadenectomy with uneventful postoperative recovery. The excised specimen was received in the department of Pathology. Gross examination of the specimen showed a grey-white area measuring 1.5 cm in diameter at the neck of gall bladder which was obstructing the lumen. Microsections examined from the grey-white area revealed mucin secreting moderately differentiated adenocarcinoma infiltrating into the wall of gall bladder. Also, foci of solid nests and trabeculae of small to medium cells with amphophilic and finely granular cytoplasm, round nuclei with salt and pepper chromatin were identified in the deeper part of same sections which showed high grade neuroendocrine carcinoma extending upto the serosal surface of the gall bladder. The tumor showed large areas of tumor necrosis and was extending to adjoining soft tissue with lymphovascular invasion. The attached portion of liver also showed tumor deposits. Five lymph nodes isolated were infiltrated by deposits of adenocarcinoma. Various immunohistochemical markers were applied which showed CK positivity in areas of moderately differentiated adenocarcinoma. Synaptophysin and chromogranin came positive in areas of tumor cells with...
neuroendocrine differentiation. Based on the histopathological findings and immunohistochemical markers, a diagnosis of mixed adeno-neuroendocrine carcinoma was made. The patient received chemotherapy after the surgery and is on regular follow-up since then.

**DISCUSSION**

Mixed adeno-neuroendocrine carcinoma is a rare entity which has been defined differently since its first definition by Cordier in 1924 and several years later by Lewin in 1987. The final description was given by WHO in 2010 as neoplasms involving both the epithelial and the neuroendocrine components and necessitates the presence of each component comprising at least 30% of the tumor and both components being malignant \[3,4\]. There is a lack of any specific radiologic or symptomatic predictors of the tumor, and so the diagnosis is made based on the histopathological findings. Although the etiopathogenesis of the tumor is not clear, immunohistochemical studies have rendered evidence that the neuroendocrine component may give rise to the adenocarcinoma component, with both of them deriving from a single stem cell \[5\]. The published literature has shown that MANECs have been identified in various localizations, with the colon and the stomach being the most common sites. Biliary mixed adeno-neuroendocrine carcinoma are exceptionally rare with an incidence ranging from 0.5 to 2% \[2\]. In some of the MANECs, the neuroendocrine and epithelial components occur in separate areas of the same lesion as was seen in our case (composite or collision neoplasms), while in others, they are diffusely and closely admixed (combined neoplasms). There are no well defined treatment guidelines for MANECs because of their rarity. Most of the researchers recommend that MANECs should be considered aggressive tumors. Some of the studies indicate that MANEC with a well differentiated neuroendocrine component should be treated as an adenocarcinoma whereas MANEC with high grade neuroendocrine component should be treated as a neuroendocrine carcinoma \[6\]. Prognosis of these tumors depends on the degree of differentiation of each of the component. MANECs have been reported to be diagnosed at advanced stages as has been our case which has invaded into the adjoining soft tissue, attached portion of liver and the surrounding lymph nodes at the time of presentation and therefore carries a poor prognosis. Patients must undergo postoperative multidisciplinary approach including chemotherapy as soon as the diagnosis is made. The effectiveness and feasibility of treatment options in patients with MANECs needs to be further explored in the larger number of cases. Through this study, we believe that a
combination of early diagnosis, surgical treatment and proper postoperative chemotherapy may contribute towards a better prognosis.

CONCLUSION

Mixed adeno-neuroendocrine carcinoma is a rare entity and MANECs of gall bladder are extremely rare. Radical cholecystectomy with lymph node dissection and hepatectomy should be performed in advanced cases. The current available literature has laid emphasis on treating the tumor based on the differentiation of the components of MANEC and that the treatment should be guided by the most aggressive histological component. Patients may benefit from pre-operative pathological diagnosis and standard neo-adjuvant chemotherapy which would also make the surgical removal of the tumor possible.

REFERENCES